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Hepatitis, interstitial nephritis and pancreatitis in association with clozapine treatment: A systematic review of case series and reports

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## **Abstract**

### **Purpose/Background**

Clozapine is the gold standard in treatment resistant schizophrenia (TRS). We sought to review data on several inflammatory effects associated with clozapine, specifically interstitial nephritis, hepatitis and pancreatitis.

### **Methods/Procedures**

We conducted a systematic review to identify studies, published up until December 2017, describing clozapine-induced hepatitis, nephritis and pancreatitis. The primary objective was to characterise the clinical characteristics associated with each of the specific inflammatory reactions to clozapine.

### **Findings/Results**

We identified 42 cases of inflammatory reactions associated with clozapine treatment- 20 cases of clozapine induced hepatitis, 11 cases of nephritis, and 11 of pancreatitis. The mean age was 38.8(SD=11.9) years. The mean dose of clozapine used was 252.4(SD=133.7) mg. Time to onset of pancreatitis (17.9(SD=11.2)(range 4-35)days) was shorter than that for hepatitis (34.2 (SD=20.1)(range=12-90)days) and nephritis (27.9(SD=27.0)(range=8-90)days), but was not statistically significant ( $F=2.267, p=0.117$ ). The mean time to recovery was shorter for cases of pancreatitis (15.7(SD=18.4)days) compared to cases of hepatitis (25.9(SD=16.5)) and nephritis (24.5(18.9)days). Three cases with hepatitis died. Seven of the cases had a clozapine rechallenge (hepatitis (n=3), nephritis (n=1), pancreatitis (n=3)), with five having a recurrence at a mean onset of 3.5(SD=2.5)days(range=1-7 days); two hepatitis cases were successfully rechallenged.

### Implications/Conclusions

Clozapine-induced hepatitis, nephritis and pancreatitis are uncommon adverse events, reflected in the paucity of case studies in the literature. Early recognition of the signs and symptoms of clozapine associated hepatitis, nephritis and pancreatitis is important, as when identified, clozapine should be urgently discontinued. Clozapine is associated with evidence of benign inflammatory processes- the extent to which hepatitis, and other inflammatory reactions, may be on a continuum with these more benign and self-limiting reactions is unclear, and this can only be resolved by prospectively following cohorts of clozapine-treated patients.

**Keywords: adverse event; side effect; antipsychotic; schizophrenia; treatment-resistant**

### Introduction

Clozapine is the most effective medication for treatment resistant schizophrenia (TRS).<sup>1</sup> As a result, it occupies a unique position in the management of schizophrenia and other psychotic disorders. However, the use of clozapine is limited by the occurrence of adverse events. Some of the more serious adverse events associated with clozapine, such as agranulocytosis and myocarditis are idiosyncratic and have similarities to hypersensitivity reactions.<sup>2-4</sup>

Clozapine is associated with nonspecific inflammatory responses in the early weeks of treatment, including benign fever, raised inflammatory markers such as C-reactive protein,

and eosinophilia.<sup>5,6</sup> Less commonly, inflammatory disorders such as myocarditis, pericarditis, serositis, interstitial nephritis, hepatitis and pancreatitis have been reported.

The demographic and clinical profile of these clozapine treated patients who develop inflammatory disorders has yet to be described in a sufficiently large sample, which has prevented clinicians from adopting an evidence-based approach to their diagnosis and management. The present study aims to address this issue through a systematic review of cases reported in the literature. Previous reviews have focused on cardiotoxicity, including pericarditis and myocarditis,<sup>7</sup> and serositis,<sup>8</sup> associated with clozapine treatment and these effects will not be revisited in this review.

## **Aims**

To gain a better understanding and awareness of clozapine inflammatory adverse effects, we conducted a systematic review to identify clinical features associated with clozapine associated hepatitis, nephritis and pancreatitis.

## **Methods**

We performed a literature search to identify peer-reviewed articles of interventional and observational studies; case series and case reports, published until December 2017, investigating or describing clozapine associated hepatitis, nephritis, and pancreatitis. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard.<sup>9</sup>

## **Inclusion criteria**

Studies and case reports of patients (no age restrictions) describing a clozapine associated hepatitis, nephritis, or pancreatitis, including patients who developed such an episode during rechallenge. We included clinically diagnosed interstitial nephritis in which evidence of acute renal failure and/or acute kidney injury were recorded with concurrent evidence of an inflammatory response, as in such cases renal biopsy is not required to confirm the diagnosis.<sup>10</sup>

## **Exclusion-criteria**

Studies were excluded: if there was evidence of clozapine associated myocarditis; if an alternative cause for the inflammatory disorder was documented; if the inflammatory disorder appeared to have occurred secondary to a different clozapine adverse event (e.g. clozapine

induced hypertriglyceridemia); if there were insufficient clinical or laboratory data to permit further evaluation of the report.

### **Information sources and searches**

Two independent reviewers (HAK and JL) performed an electronic search using PubMed, Medline, Scopus, EMBASE and Google Scholar from inception until December 2017. The following search terms were used, alone and in combination: clozapine AND hepatitis or nephritis or pancreatitis. In addition, the reference lists of the retrieved articles and relevant review articles were examined for further reports.

### **Study selection and exclusion**

All extracted reports were examined independently by two authors (HAK and JL) and a list of full text articles established. Authors were contacted for clarification where necessary.

The study selection process, search results, and reasons for exclusion are given in figure 1. The initial search yielded 127 references. After checking titles and abstracts, 59 full texts were screened and 41 of these (42 patients) were included for data extraction. All were case series or reports; no interventional or observational studies were identified.

### **Data extraction**

The primary objective was to characterise the clinical characteristics associated with each of the specific inflammatory disorders, including the time to recovery and mortality associated with the systemic inflammatory disorder.

Where available, we extracted demographic data (gender, age and ethnicity) and relevant laboratory data including: White cell counts (WCCs), neutrophil counts, lymphocyte counts, eosinophil counts, C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), renal function tests (serum creatinine levels), Liver Function Tests (Alkaline phosphatase (ALP), Aspartate Aminotransferase (AST), Gamma-glutamyl transpeptidase (GGT)) and serum bilirubin; amylase level, lipase level, and urinalysis. We recorded information on: timing of the onset of the inflammatory disorder relative to clozapine initiation, clozapine dose used, plasma clozapine and norclozapine concentrations, concurrent medications used concomitant disease, and smoking. We examined presenting signs and symptoms, management, time to recovery, and mortality associated with the inflammatory disorder.

## **Results**

**Demographic and clinical characteristics of all included cases of clozapine induced systemic inflammatory disorders.**

There were 41 qualifying reports, all of which were case reports. In total 42 patients were identified who developed a clozapine associated hepatitis, nephritis, or pancreatitis.

We identified 20 cases of clozapine induced hepatitis,<sup>11-30</sup> 11 cases of nephritis,<sup>31-41</sup> and 11 of pancreatitis.<sup>42-52</sup> Demographic and clinical characteristics of all identified cases are shown in table 1.

Forty eight percent of the cases were of White ethnicity (n=11), 44% were of Asian ethnicity (n=10), and one was of Black ethnicity and one of mixed ethnicity. Most the cases identified had a diagnosis of schizophrenia (76%; n=32). Fourteen percent had a diagnosis of schizoaffective disorder (n=6), with 3 cases of bipolar affective disorder and one case of psychosis in Parkinson's disease.

### **Clinical characteristics of all cases**

The mean dose of clozapine used was 252.4mg (SD=133.7). In three cases (two hepatitis and one pancreatitis case respectively) plasma clozapine concentrations were recorded, and were above the therapeutic range in all cases, with a mean plasma clozapine concentration of 0.87 mg/L (range 0.831-0.910mg/L).<sup>17, 24, 43</sup> In two of the cases plasma norclozapine was recorded with a mean level of 0.23 mg/L (range 0.21-0.24 mg/L) The mean duration of clozapine use prior to the onset of the systemic inflammatory disorder was 28.3 (SD=21.0) days (median=24.5 days; range 0-90 days).

Where concomitant medication was reported, 6 out of 10 patients with nephritis, 1/4 with hepatitis, and 1/3 with pancreatitis were concurrently treated with lithium carbonate; 6/10 with nephritis, 2/4 with hepatitis, and 1/3 with pancreatitis were concurrently treated with sodium valproate.

Fever (>38 °C) was reported in ninety percent of cases (n=18/20), eosinophilia in 86% (n=19/22). Twelve cases had multiple internal organ involvement. (n=5 with hepatitis (liver and respiratory involvement (n=4); liver, kidney and respiratory involvement (n=1)); n=4 with nephritis (kidney and respiratory involvement in all 4 cases); and n=3 with pancreatitis (pancreatic and liver involvement (n=2); and pancreatic and kidney involvement (=1)).

CRP was reported in 9 cases, all of which were raised (n=2 hepatitis; n=4 nephritis; n=3 pancreatitis). The mean CRP level was 116.9 (SD=94.5) (range 7.0-297.4) mg/L. Only three reports commented on cutaneous involvement, with two cases having a skin rash. The presence or absence of lymphadenopathy or atypical lymphocytes was not determined in any of the cases.

## Recovery and mortality

The mean time to recovery in 27 cases was 23.0 (SD=17.4) days (median=17 days; range=3-62 days). The duration to recovery for those treated with clozapine and valproate (mean=16.7 (SD=3.8) days) was longer compared to those not co-treated with valproate (mean=9.0 (SD=5.8) days;  $t=1.964$ ,  $p=0.107$ ). Clozapine associated pancreatitis had a non-statistically significant shorter time to recovery compared to hepatitis cases (mean difference -16.3 days,  $p=0.097$ , 95%CI: -34.9-2.4) and nephritis cases (mean difference -10.8 days,  $p=0.490$ , 95%CI: -31.2—11.2).

Death was reported in three cases of clozapine induced hepatitis.<sup>18, 26, 29</sup>

## Clozapine rechallenge

Seven of the cases underwent a clozapine rechallenge (hepatitis  $n=3$ ,<sup>11, 12, 15</sup> nephritis  $n=1$ <sup>35</sup>, pancreatitis  $n=3$ <sup>45, 50, 51</sup>). Five of the cases had a recurrence of the incident inflammatory disorder, at a mean onset of 3.5 (SD=2.5) days (range=1-7 days) which was significantly shorter than those who were treated with clozapine for the first time (mean=27.0 (SD=19.0) days (range=0-90 days)) ( $t=-2.418$ ,  $p<0.019$ ). The mean time to recurrence in pancreatitis rechallenge was 3.7 (SD=3.1) days (range 1-7); the time to recurrence in a single nephritis case was 3 days. Two of the cases of clozapine associated hepatitis were successfully rechallenged.<sup>12, 15</sup>

## Treatment of nephritis

The most comprehensive treatment documentation was recorded in nephritis cases. Of those with clozapine associated nephritis, 46% ( $n=5/11$ ) were treated with steroids ( $n=2$  with methylprednisolone 1g/day for 3 days, followed by oral prednisolone), with prednisolone used in all five cases (dose range 25-30mg/day in those in which it was recorded); and 27% ( $n=3/11$ ) receiving haemodialysis.

## Discussion

Our review findings provide the largest synthesis of cases of clozapine associated hepatitis, nephritis and pancreatitis. The presenting symptoms and signs in most cases were vague, and related to internal organ involvement. Most cases presented with eosinophilia and fever, along with raised transaminases in hepatitis, raised creatinine in nephritis and raised lipase (and/or amylase) in pancreatitis. Fever was seen in the majority of cases, along with raised CRP and eosinophilia, all indicative of hypersensitivity. CRP was elevated in all cases in

which it was reported, but the majority of cases did not report CRP levels. More than one organ was involved in 47% of cases.

### **Clozapine associated hepatitis**

Liver involvement was characterised by fever, abdominal pain and non-specific symptoms such as nausea, and lethargy, with jaundice occurring in a minority of cases. All cases had clinically significant elevated transaminases (ALT and/or AST > 3 fold above the upper limit of normal (ULN)<sup>53</sup>), and evidence of eosinophilia, with over 50% with elevated serum bilirubin (> 2 fold above the ULN). The onset of hepatitis was within 8 weeks of clozapine initiation in all but three cases (onset at 60, 63 and 90 days respectively) with a mean time to onset of 34.2 days. The average time to recovery was 25.9 days. Fifty percent of hepatitis cases had other internal organ involvement, and it was associated with death in three cases. The mean ALT value of 629 U/L is consistent with findings in drug induced liver failure in which the elevation in ALT and/or AST at 500-600 IU/L is less marked when compared to other causes, such as paracetamol toxicity, or viral hepatitis (such as hepatitis A or B).<sup>54</sup> Drug induced liver injury is responsible for approximately 2- 13.9 cases per 100,000 people per year.<sup>55, 56</sup> Previous studies comparing differential effects of antipsychotics on liver function, identified that clozapine was most frequently associated with abnormal LFTs.<sup>57-59</sup> A systematic review identified a median rate of clozapine associated clinically significant elevations in LFTs (> 2 fold ULN of AST and/or ALT) of 16.7%, though this was not equivalent to severe liver injury in the majority.<sup>59</sup> The mechanism for benign changes in LFTs relating to clozapine use, may be related to indirect mechanisms such as comorbid alcohol use and alcohol fatty liver changes, weight gain and metabolic syndrome,<sup>60</sup> whereas the more severe inflammatory response identified in this review is postulated to be an immune mediated hypersensitivity phenomenon.<sup>6, 59</sup>

### **Clozapine associated nephritis**

Nephritis was characterised by fever, gastrointestinal symptoms, tachycardia and urinary difficulties. The classic clinical triad of rash, fever, and eosinophilia was not present, with a rash not documented in any cases, suggesting that clozapine-associated nephritis differs from classical nephritis. Creatinine was raised in all cases, as was CRP (reported in four cases only) and proteinuria was seen in most cases. The onset of nephritis was within 3 weeks of clozapine initiation in 73% of cases, with the other 3 cases having onset at 45-90 days. The time to recovery was less than 4 weeks for all but one, in which the time to recovery was 61 days.



Of suspected clozapine adverse events reported to the United Kingdom Medicines and Healthcare products Regulatory Agency (n=26,000), 10 were of acute interstitial nephritis and 31 of acute renal failure,<sup>35</sup> indicating that it is a low prevalence event, which is indicated by the low number of cases identified in our review.

### **Clozapine associated pancreatitis**

Pancreatitis was characterised by fever, abdominal pain, and distension, with nausea and vomiting. All cases had abnormal amylase and/or lipase measures, and raised CRP. Twice as many people had raised lipase compared to amylase. Clozapine associated pancreatitis was identified earlier than the onset of nephritis or hepatitis, with a mean onset of 18 days (all cases with onset within 5 weeks of clozapine initiation), although this may reflect the fact that pancreatitis was the most symptomatic of the three disorders. In pancreatitis lipase and amylase tend to rise within the first few hours of symptom onset, with lipase remaining elevated for longer than amylase levels.<sup>61</sup> It is important to note that in up to 25% of cases serum amylase or lipase levels will not be elevated, necessitating need to consider imaging studies if the clinical presentation is suggestive of pancreatitis.<sup>61</sup>

In our review, clozapine associated pancreatitis had a shorter duration of recovery (15.7 days) compared to hepatitis and nephritis cases. A Swedish Nationwide database study identified an increased risk of pancreatitis with antipsychotic use, though this was not increased with clozapine or olanzapine use (OR 0.9 (0.6-1.4)).<sup>62</sup> Drug induced pancreatitis is responsible for up to 2% of acute pancreatitis, necessitating consideration for alternative causes.<sup>63</sup> Alcohol abuse is common in schizophrenia, and is a potential aetiology for clozapine associated pancreatitis, associated with up to 30% of pancreatitis cases in the general population<sup>63</sup>. Assessment for hyperglycaemia and hypertriglyceridaemia are indicated in cases of clozapine induced pancreatitis, as both are risk factors for pancreatitis and can be raised early in the course of clozapine use.<sup>64-66</sup> In a pharmacovigilance survey and literature review, 16 clozapine associated pancreatitis cases were identified occurring in the context of recently diagnosed hyperglycaemia<sup>67</sup>. If indicated, appropriate treatment of hyperglycaemia with insulin therapy should be initiated, with antibiotic therapy indicated if infection is identified. A systematic review of the FDA's MedWatch database found that sodium valproate was used in 34% (n=22/64) of clozapine associated pancreatitis cases,<sup>67</sup> while 1 case from 3 pancreatitis cases were treated with sodium valproate in our review.

### **Clozapine dose effect**

A casual association between clozapine and hepatitis, nephritis and pancreatitis is strongly suggested by timing of the adverse reaction, and recovery on discontinuation of clozapine.

No conclusions can be drawn about a dose-effect relationship, as the systemic inflammatory process occurred in most cases at a clozapine dose of < 400mg daily. However, the mean plasma concentration of clozapine was 0.9 mg/L in 3 cases in which it was recorded, with all those cases treated with 300mg daily of clozapine. All cases in which plasma clozapine concentration was recorded had evidence of supratherapeutic plasma clozapine concentrations. This may have been artefactual, related to impaired clozapine metabolism due to hepatic dysfunction or impaired elimination.<sup>68</sup> Alternatively, such elevated clozapine plasma levels may be a contributory factor to clozapine systemic inflammatory disorders.

### **Clozapine rechallenge following clozapine-associated inflammatory reactions**

There have been a few reported cases of clozapine rechallenge after an episode of clozapine associated hepatitis (n=3), nephritis (n=1) or pancreatitis (n=3).

#### ***Rechallenge following clozapine associated hepatitis***

Two of the clozapine associated hepatitis cases were successfully rechallenged with clozapine. In the first, clozapine was titrated to 300mg daily (during the initial clozapine trial the patient was treated with 175mg daily in combination with sodium valproate 1000mg twice daily) with no recurrence of hepatitis<sup>15</sup> at 36 months follow up. Sodium valproate was not used during rechallenge, suggesting that it may have contributed to the incident hepatitis. In the other successful clozapine rechallenge following hepatitis, LFTs were monitored three times weekly, and rose to ALT 208U/L, AST 109U/L at day 20 while treated with clozapine 500mg/day. Clozapine (concurrent medication use not recorded) was continued at a reduced dose of 400mg /day and LFTs normalised, with clozapine maintained at 9 months follow up with normal LFTs.<sup>12</sup>

#### ***Rechallenge following clozapine associated nephritis***

One case of clozapine induced nephritis was rechallenged with clozapine. In this 25 year old, there was a recurrence of nephritis, with fever, tachycardia, markedly raised CRP (197 mg/L) and a rising creatinine, all occurring within 3 days of clozapine (dose 25mg/day) rechallenge.<sup>35</sup>

#### ***Rechallenge following clozapine associated pancreatitis***

Three cases of clozapine associated pancreatitis were unsuccessfully rechallenged with a recurrence of pancreatitis within 7 days in all cases.

In the first, clozapine was reinitiated 18 months after the index episode (time to onset 27 days).<sup>51</sup> Prior to clozapine rechallenge there were two separate records of mildly elevated

lipase (299 IU/L and 273 IU/L). Clozapine 12.5mg twice daily was administered for one day before the onset of right upper quadrant pain, nausea and vomiting. A serum lipase of 546 IU/L and a mild eosinophilia were seen. Clozapine was discontinued and symptoms did not recur, with serum lipase returning to pre- clozapine levels in 3 weeks.

In the second rechallenge, clozapine was started 7 days after the initial clozapine associated pancreatitis.<sup>50</sup> Three days after clozapine initiation, the patient had abdominal pain and distension, and ileus, with a recorded serum amylase of 379 IU/L and lipase 485 IU/L. Clozapine was discontinued, and over the next 7 days symptoms gradually resolved and serum lipase and amylase levels normalised.

In the final case, clozapine was reinitiated at an unspecified time after the index episode (time to onset 30 days and a plasma clozapine concentration of 831mg/L).<sup>45</sup> One week after clozapine initiation and at a dose of 100mg daily, there was an elevation in glucose and pancreatic enzymes (level not specified, though they were less marked than index episode lipase level of 759 IU/L). Clozapine was discontinued and the patient was treated with antibiotics and insulin regimen.

In the five unsuccessful rechallenge cases, the onset of the systemic inflammatory disorder was earlier than that seen in people treated with a first clozapine trial, consistent with a hypersensitivity reaction.

### **Relationship with nonspecific inflammatory reactions to clozapine**

It has been shown that clozapine treatment is frequently associated with transient and apparently benign pyrexia, often accompanied by eosinophilia and elevations in C-reactive protein and other non-specific inflammatory markers, early in the course of treatment.<sup>5, 6</sup>

This inflammatory response usually resolves spontaneously despite continuation of clozapine treatment. Other studies have shown asymptomatic and benign elevations in transaminases and ALP (>2 fold above upper limit of normal) in up to 40% of clozapine treated patients,<sup>58</sup> which also seem to be transient, with 60% normalising within 13 weeks despite continued clozapine treatment.<sup>57</sup>

We therefore consider it probable that some, or even the majority, of patients with non-specific inflammatory responses may also have transient elevations in liver enzymes, which are not identified since liver function tests are rarely ordered. The extent to which hepatitis, and other inflammatory reactions, may be on a continuum with these more benign and self-limiting reactions is unclear, and this can only be resolved by prospectively following cohorts of clozapine-treated patients.

## Limitations

Limitations include the retrospective review of case reports, and the large amount of missing data in the included reports, inconsistencies between laboratory norms for the relevant investigations, and inconsistent reporting of signs and symptoms. There were no controlled studies available, and there is a need for caution in interpreting data relating to case reports and case series.<sup>69</sup> Case reports alone cannot provide an accurate or quantitative estimate of the risk for complications or death associated with a drug or treatment intervention such as this. Publication bias may have affected the cases reported: for example, successful rechallenge may have been more likely to have been reported than failed rechallenge. Further, details on clinical outcome and therapeutic interventions was often lacking in the included case reports. Finally, we restricted our search to peer-reviewed reports, ensuring that all included studies have been peer reviewed, but meaning that we may have missed studies from the 'grey literature'. It is likely that clozapine associated hepatitis, pancreatitis and nephritis occurs more frequently than is indicated in our review and which may be reflected in increased content in the 'grey' literature.

## Implications for clinical practice

Notwithstanding the limitations above, this review gives an indication of the clinical picture associated with each of the individual disorders. The results have some implications for practice.

Clinicians should be aware of the potential for hepatitis, nephritis or pancreatitis with clozapine use which should prompt withdrawal of clozapine if it is identified as the offending agent, with referral to general medical teams if required. It seems prudent to measure baseline renal function and LFTs as part of a pre-clozapine work up, so that any subsequent elevation can be quantified. While there seems insufficient evidence to support the routine monitoring of LFTs (transaminases), renal function, pancreatic enzymes in standard monitoring protocols, any emergence of fever, eosinophilia or markedly raised CRP (> 50 mg/L), should be followed with checks of LFTs, renal function, and serum lipase, to ensure that no covert inflammatory process is occurring.

In our review, there was insufficient data provided in the identified cases to draw any inferences about the treatment of the clozapine associated inflammatory disorder.

## Rechallenge

Successful clozapine rechallenge has been implemented with haematopoietic support in clozapine agranulocytosis,<sup>70</sup> but in systemic inflammatory disorders, there appears to be a high risk of recurrence where there is evidence of autoimmune involvement, with fever and eosinophilia and multiorgan involvement. We found insufficient information to make inferences about rechallenge other than the observation that successful rechallenge is possible in some cases. Clinicians need to remain aware of the potential for a more rapid onset of symptoms following a rechallenge.

## Conclusion

Our systematic review confirms that clozapine associated inflammatory disorders are not commonly reported in the literature, likely a reflection of their low incidence. The occurrence of abnormal blood parameters and /or symptomatic liver, kidney, or pancreatic injury should prompt withdrawal of clozapine and full assessment. The discontinuation of clozapine remains the cornerstone of management in such cases with most cases reaching full recovery following discontinuation. Future research might focus on the underlying mechanisms of drug hypersensitivity reactions, and their relationship to more benign and transient reactions, to better understand the aetiology of clozapine associated systemic inflammatory disorders and other hypersensitivity reactions.

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**Table 1**

**Baseline characteristics of individual case reports of clozapine induced hepatitis, nephritis and pancreatitis (total n=42)**

	All cases	Hepatitis	Nephritis	Pancreatitis
Gender	21 males 21 females	9 males 11 females	6 males 5 females	6 males 5 females
Mean age (SD) years	38.8 (11.7) (range 17-73)	40.4 (9.9)	35.9 (12.6)	38.7 (14.6)
Mean clozapine dose (mg) (SD)	252.4 (133.7)	298.7 (92.2)	211.4 (179.7)	213.6 (127.7)
Mean plasma clozapine/norclozapine concentration (mg/L) (SD)	0.87 (0.04)/ 0.23 (0.02)	0.905 (0.01) (n=2) /0.21	N/A	0.831/0.24 (n=1)



Mean time to onset (days) (SD) (range) F=2.267, p=0.117	28.3 (21.0) (0-90)	34.2 (20.1), (12-90)	27.9, (SD=27.0), (8-90)	17.9 (11.2), (4-35)
Clinical presentation		Fever: 88.9% Lethargy: 33.3% Jaundice: 22.2% Abdominal pain: 22.2% Nausea: 22.2%	Fever:100% Tachycardia: 36.4% Vomiting:27.3% Diarrhoea :27.3% Nausea: 18.2% Urinary difficulty :18.2%	Fever:75% Abdominal Pain:46.6% Nausea: 23.1% Vomiting: 23.1% Abdominal distension:15.4%
Laboratory data		Raised CRP 100 % Mean ALT level: 628.8 (SD=571.1) IU/L ALT > 3 fold upper limit of normal(ULN): 85.0% (n=17/20) Mean AST level: 318.7 (SD=266.8) IU/L AST >3-fold ULN: 72.2% (n=13/18) Raised bilirubin > 2 ULN: 9/16 (56.3%) Raised eosinophils: 100%	Raised CRP:100 % (range=58.0-294.0mg/L) Proteinuria: 72.7% Mean Serum creatinine: 499.5 (371.9) umol/L Raised eosinophils: 85.7%	Raised CRP:100% (range=7.0-82.5mg/L) Mean Amylase level:344.8 U/L Mean Lipase Level: 1643.3 (1628.3) U/L Raised amylase > 3 ULN: 31% (n=4/13) Raised lipase > 3 ULN: 78% (n=7/9) Raised eosinophils:60%
Mean time to recovery (days) (SD) (range) F=0.822, p=0.451	23.0 (17.4) (3-62)	25.9 (16.5), (7-62)	24.5 (18.9), (10-61)	15.7 (18.4), (3-56)

**ULN= Upper limit of normal**

Table 2 Summary of findings

We identified 42 cases of clozapine associated hepatitis (n=20), nephritis (n=11) and pancreatitis (n=11)

The time to onset was 19 days for pancreatitis, 28 days for nephritis and 31 days for hepatitis

No clozapine dose effect was identified

Time to recovery was shortest for clozapine associated pancreatitis (16 days) compared to hepatitis (26 days ) and nephritis (25 days)

Three cases of clozapine hepatitis were fatal

Recurrence occurred in two pancreatitis cases, 1 hepatitis case and 1 nephritis case, with two hepatitis cases successfully rechallenged



